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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/697,995	10/30/2003	Dorothea Reilly	11669.195USU1	7395

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EXAMINER	
CROWDER, CHUN	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/697,995	REILLY ET AL.	
	Examiner	Art Unit	
	Chun Crowder	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05/05/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-120* is/are pending in the application.

4a) Of the above claim(s) *1-54,86-102 and 115-120* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55-85 and 103-114* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED CATION

1. The instant application appears to be in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

2. Applicant's election with traverse of Group II and species of antibody specific for VEGF, *E.Coli* host cells, DsbA and the heavy and light chains are encoded by a single polynucleotide, filed 05/05/2006, is acknowledged.

It is noted that applicant failed to elect species of one specific product (e.g. antibody with specific subtype IgG1) set forth in paragraph 10 of the Office Action mailed 03/22/2006.

During a telephone conversation with applicant's representative Katherine Kowalchyk on 06/20/2006, a provisional species election was made to prosecute antibody with IgG1 subtype. Affirmation to this election must be made by applicant in respond to this Office Action.

The traverse is on the ground that search for Group III, claims 115 and 117-120 and Group IV, claim 116 would not be unduly burdensome. This is not found persuasive because Groups I and III/IV are related as product and process of use. The examiner has shown in the Office Action, mailed 03/22/2006, that the inventions are by distinct by demonstrating the product as claimed can be used in a materially different process of e.g. affinity purification in addition to methods of treating and diagnosing. In addition, they have acquired a separate status in the art as shown by different classification and/or recognized divergent subject matter. It is an undue burden on the Examiner to search more than one invention.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-120 are pending.

Claims 1-54, 86-102, and 115-120 have been withdrawn from further consideration by the Examiner, under 37 C.F.R. 1.142(b), as being drawn to nonelected inventions.

Claims 55-85 and 103-114, read on a polynucleotide encoding an antibody IgG1, a vector, *E.Coli* host cells, DsbA, and the heavy and light chains are encoded by a single polynucleotide and a method of producing the antibody, are currently under consideration.

3. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. The priority application USSN 60/422,952 upon which benefit is claimed appears to provide adequate support under 35 U.S.C. 112 for subject matter claimed in the instant application.

4. Applicant's IDSs, filed 06/25/2004, 10/20/2004, and 05/02/2006, are acknowledged and have been considered.

5. The application is required to be reviewed and all spelling, TRADEMARK, and like error corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent application, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate correction is required.

6. Claims 63 and 64 are objected to because of the following informalities. The claims recite "DsbA, DsbC...". It is suggested that applicant amend the claims to recite the full name of the "Dsb".

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 55, 58-85, and 103-114 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 55 and 58-65 are indefinite in that they depend on non-elected claims. Applicant should amend the claims as independent from non-elected claims.

B) Claims 66-85 and 103-114 are indefinite in the recitation of "The method" in the preamble without setting forth and distinctly claiming the subject matter of the claimed invention.

C) Claim 113 is indefinite in the recitation of "The amount of claim 112" because the metes and bounds of "The amount of claim 112" is unclear and ambiguous. Applicant is invited to clarify whether claim 113 is "The method of 113...".

D) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 55-85 and 103-114 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The following *written description* rejection is set forth herein.

The specification broadly describes and the claims recite as part of the invention "a polynucleotide encoding the antibody or immunocojugate".

The specification does not appear to describe any "a polynucleotide encoding the antibody or immunocojugate".

The specification as filed does not disclose a sufficient number of species to support the "polynucleotide" as broadly encompassed by the claimed invention.

Rather, the instant specification appears to describe the written description of the cDNAs corresponding to the particular antibodies (e.g. anti-tissue factor antibody and anti-VEGF antibody. See Examples on pages 57-67 of the instant specification).

In addition, the claimed polynucleotide would encompass genes or continuous or discontinuous regions of nucleic acids encoding an antibody. The claimed products may also contain additional coding and non-coding regions and, in turn, encompass the "gene". In addition, the invention could embrace any substitution, insertion or deletion change of nucleotides throughout the entire stretch of the polynucleotide encoding any antibody that has any antigen specificity.

It is well known that antibody diversity is critical and evident for a proper immune response, including making antibodies of interest. During B cell differentiation, antibody diversity is generated in the heavy and light chains of the immunoglobulin by mechanisms including multiple germ line variable (V) genes, recombination of V gene segments with joining (J) gene segments (V-J recombination) and recombination of V gene segments with D gene segments and J gene segments (V-D-J recombination) as well as recombinational inaccuracies. Furthermore, somatic point mutations that occur during the lifetime of the individual, immunized individual (e.g. immunized mouse for hybridomas) or a cell line also lead to antibody diversity. Thus, a huge number of different antibody genes coding for antibodies with exquisite specificity can be generated. The total potential immunoglobulin repertoire exceeds 10^{11}.

Therefore, given the well known polymorphism of immunoglobulins/antibodies; applicant was not in possession of the vast repertoire of "a polynucleotide encoding the antibody or immunocojugate".

Applicant was not in possession of the structural attributes of a representative number of species pollessed by the member of the genus of "a polynucleotide encoding the antibody or immunocojugate".

Such polynucleotides do not meet the written description provision of 35 U.S.C. 112 first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

The specification as filed does not provide written description support for any "a polynucleotide encoding the antibody or immunocojugate". The skilled artisan cannot envision all the contemplated nucleotide sequences by the detailed chemical structure of the claimed "a polynucleotide encoding the antibody or immunocojugate", especially when antigen specificity was not provided. Therefore, conception cannot be achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483.

Again, in the instant case; the specification provides only written description for methods of isolating specific polynucleotides encoding antibodies (e.g. anti-tissue factor antibody and anti-VEGF antibody. See Examples on pages 57-67 of the instant specification), and appropriate host cells and vectors, but not the full breadth of he claimed "polynucleotide encoding the antibody or immunocojugate".

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 55-59, 65-86, and 104 are rejected under 35 U.S.C. 102(b) as being anticipated by Gillies et al. (Human Antibody Hybridomas. 1990 1;1:47-54. Cited on IDS filed 05/02/2006) (see entire document) and Davis et al. (The EMBO Journal 1989. 8;9:2519-2526. Reference cited on IDS filed 06/25/2004) (see entire document).

Gillies et al. teach methods of making mutant chimeric antibodies with human tumor specificities. Specifically, Gillies et al. teach methods of constructing vectors with two chimeric antibodies with anti-tumor specificity wherein the chimeric antibodies carry the following mutations: A) entire CH2 domain is deleted, and B) two hinge cysteine residues involving in the inter-heavy chain disulfide bond formation are mutated to serines (see entire document, particularly Materials and Methods on pages 48-52). Gillies et al. further teach methods of making the mutant antibody using host cells (e.g see pages 48-49). Furthermore, Gillies et al. teach that the mutant antibody has normal antigen binding activity but greatly reduced ADCC and CDC (e.g. see Discussion on pages 52-54).

Davis et al. teach methods of making IgM variant by replacing cysteine residues responsible in forming inter-heavy chain disulfide bonds at position 337, 414, and 575 with serine (see entire document, particularly page 2519). Davis et al. further teach methods of making the IgM variant using recombinant plasmid vector containing the polynucleotide encoding the antibody variant and host cells.

Therefore, the reference teachings anticipate the claimed invention.

13. Claims 55-85 and 103-114 are rejected under 35 U.S.C. 102(e) as being anticipated by Simmons et al. (US Patent Application 2005/0170464) (see entire document).

Simmons et al. teach methods of producing and purifying antibodies, immunoconjugates and their variants in prokaryotic host cells. Specifically, Simmons et al. teach that polynucleotides encoding antibodies including human IgG1 can be cloned into recombinant vectors and expressed in prokaryotic host cells such as *E.Coli.* carrying different plasmid encoding different enzymes such as Dsb proteins (see entire document, particularly Examples on pages 18-28). Simmons et al. further teach that the antibodies or immunocojugates can be variants with amino acid substitutions in the Fc regions and any cysteine residue may be substituted with serine to improve the oxidative stability and prevent aberrant crosslinking (e.g. see pages 12-15).

Given the that the amino acid sequences of the Fc regions including the hinge regions were well known in the art, one skill artisan would immediately envisage that Simmons et al. taught the amino acid substitution from Cysteine to Serine in the Fc region including the those cysteine residues in the hinge region that are responsible forming inter-heavy chain disulfide bonds.

In addition, the claimed limitation of less self aggregation of the variant would be inherent properties of the reference antibody.

Therefore, the reference teachings anticipate the claimed invention.

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 55-85 and 103-114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gillies et al. (Human Antibody Hybridomas. 1990 1;1:47-54. Cited on IDS filed 05/02/2006) and Davis et al. (The EMBO Journal 1989. 8;9:2519-2526. Reference cited on IDS filed 06/25/2004) in view of Georgiou et al. (US Patent 5,264,365. Reference cited on IDS filed 10/20/2004) and Kurokawa et al. (The Journal of Biological Chemistry. 2001. 276;17:14393-14399).

The teachings of Gillies et al. and Davis et al. have been discussed, supra.

The reference teachings differ from the claimed invention by not describing *E.Coli* host cells with DsbA and deficient in endogenous protease activities.

However, methods of making heterologous proteins using modified prokaryotic host cell such as certain *E.Coli* strains were well known in the art at the time the invention was made. For example, Georgiou et al. teach methods of making recombinant proteins using protease deficient *E.Coli* strain (see entire document, particularly Summary of the Invention on columns 2-6). Georgiou et al. further teach using *E.Coli* strain deficient in proteases as host cells for producing recombinant protease sensitive proteins such as antibody fragment provides inexpensive ways of producing recombinant proteins in large quantity, correct folding, and reduced protein degradation (e.g. see columns 1-2, in particular).

Kurokawa et al. teach that the periplasm of *E.Coli* contains enzymes that can assist protein folding such as disulfide bond formation proteins Dsb and over-expression of Dsb proteins can increase efficiency of periplasmic expression of heterologous proteins with multiple disulfide bonds in *E.Coli* (see entire document, particularly pages 14393-14394).

It would thus have been obvious to the ordinary artisan at the time the invention was made to make antibody comprising a variant heavy chin hinge region incapable of inter-heavy chain disulfide linkage using *E.Coli* strain with Dsb proteins and deficient in proteases. The ordinary artisan would have been motivated to produce the antibody variant using *E.Coli* strain expressing Dsb proteins and deficient in proteases because Dsb proteins can increase efficiency of periplasmic expression of heterologous proteins with multiple disulfide bonds and *E.Coli* strain deficient in proteases can provide inexpensive ways of producing recombinant proteins in large quantity, correct folding, and reduced protein degradation.

Given the teachings of Gillies et al. and Davis et al. regarding methods of making antibody variant incapable of forming inter-heavy chain disulfide linkage, and the teachings of Georgiou et al. and Kurokawa et al. providing methods of making antibody using E. Coli strains with Dsb proteins and deficient in proteases, the ordinary artisan at the time the invention was made would have had a reasonable expectation of success of producing antibody variant incapable of inter-heavy chain disulfide linkage formation using E. Coli strains with Dsb proteins and deficient in proteases.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chun Crowder whose telephone number is (571) 272-8142. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chun Crowder, Ph.D.
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June 22, 2006

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